UNIVERSITI TEKNOLOGI MARA

THE EFFECT OF ACUTE AND CHRONIC EXOGENOUS LEPTIN ADMINISTRATION ON GLUT4 EXPRESSION AND PLASMA GLUCOSE UPTAKE IN THE RAT

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AUTHOR'S DECLARATION

I declare that the work in this thesis dissertation was carried out in accordance with the regulation of University Technology MARA. It is original and is the results of my one work. Unless otherwise indicated or acknowledgment as referenced work. This thesis has not been submitted to any other academic institution or non-academic institution for my degree or qualification

I, hereby, acknowledge that I have been supplied with Academic Rules and Regulation for post academic, University Technology MARA. Regulation the conduct of my study and research.

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ABSTRACT

Acute leptin administration to rats inhibits insulin secretion either through centrally or peripherally mediated mechanisms. But type 2 diabetic obese individuals with impaired glucose utilization are also hyperleptinemic, which suggests that leptin action might depend on the duration of exposure to hyperleptinemia. This study examined the difference in blood glucose homeostasis following acute and chronic leptin administration in rats. Glucose tolerance curves were plotted for 14-week old male Sprague-Dawley rats treated with either normal saline (Control; n=8) or a single leptin injection (60ug/kg body weight - acute leptin; n=8) or subcutaneous leptin injections for 42 days (60 ug/kg body weight/day-chronic leptin; n=8). Following this, the rats were anaethetised with thiopentone sodium (100 mg/kg/body weight) and infused intravenously with 50 mg of glucose in water at a rate of 100 µl/min for 5 minutes. Arterial blood samples were collected every 5 mins for the first 30 minutes for glucose estimation. Data were analysed using repeated measures MANOVA or one-way ANOVA with post-hoc analysis, and presented as mean ± SEM. Glucose clearance in acute leptin-treated rats did not differ from the controls. However, there was an overall significant decrease in plasma insulin levels with improved insulin sensitivity. This was achieved by increased insulin receptor expression whilst maintaining normal GLUT4 levels mainly through effective translocation from the GLUT4 vesicles. Compared to the acute leptin-treated rats, chronic leptin-treated animals had significantly higher blood glucose levels and hyperinsulinemia after glucose challenge. Chronic leptin administration decreased insulin sensitivity index by inhibiting the expression of insulin receptor. Conclusion it appears that the role of leptin in glucose clearance might be related to the duration of exposure to leptin. Acute leptin administration inhibited insulin secretion while maintaining normal glucose homeostasis by increasing insulin sensitivity by 1) increasing the expression of insulin receptor in the skeletal muscle, 2) by effectively maintaining GLUT4 translocation from the storage vesicles probably mediated by PI3K pathway. Chronic administration of leptin for 42 days induced insulin resistance by decreasing the expression of insulin receptors in the insulin sensitive tissues. This resulted in the compensatory hyperinsulinemia. Since the chronic study was designed to mimic the chronic elevation of leptin or hyperleptinemic state in obese individuals, the findings from our study suggest that hyperleptinemia decreases expression of insulin receptors in insulin-sensitive tissues and thus promotes insulin resistance.

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